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REMARKS

The present invention relates generally to providing fluorescent particles useful in determining analyte concentrations in aqueous solutions. The particles of the present invention incorporate dye pairs that are selected to provide advantageously large Stokes shifts (i.e., the shift in wavelength between peak light absorption and peak fluorescent emission) through resonant energy transfer between the members of the dye pairs. *See, e.g.*, specification, page 13, lines 5-23. In addition, the fluorescent particles of the present invention can provide reduced quenching of the fluorescent signal. *See, e.g.*, specification, page 14, lines 12-18.

Claims 30-46 are presently pending in the application, with claims 30, 31, 42 and 45 presently under consideration by the Examiner, and claims 32-41, 43, 44 and 46 removed from consideration by restriction requirement. However, in a personal interview, the Examiner indicated that the withdrawn claims would be reconsidered should generic claim 30 be found to be allowable in accordance with MPEP § 809.

Applicants respectfully request reconsideration of the claims in view of the following remarks.

Non Art-Related Remarks

Restriction/Election

In their previous response, Applicants noted that the Examiner has required a species election in dependent claims 32-41, 43-44, and 46, which are within the scope of independent claim 30. In a personal interview, the Examiner indicated that the withdrawn claims would be reconsidered should generic claim 30 be found to be allowable in accordance with MPEP § 809.

Art-Related Remarks

Information Disclosure Statement

Applicants submit herewith the Information Disclosure statement requested by the Examiner.

35 U.S.C. § 103

Applicants respectfully traverse the rejection of claim 30 as allegedly being unpatentable under 35 U.S.C. § 103(a) over Sounik *et al.*, EP 0391284, and Wheeler *et al.*, *J. Am. Chem. Soc.* 106: 7404-10 (1984). Applicants submit that the Examiner has not established a motivation to combine the publications as suggested by the Examiner. Moreover, even if combined as suggested, the publications do not teach or suggest each and every element of the present claims. Thus, no *prima facie* case of obviousness has been established.

To establish a *prima facie* case of obviousness, three criteria must be met; there must be some motivation or suggestion, either in the cited publications or in knowledge available to one skilled in the art, to modify or combine the cited publications; there must be a reasonable expectation of success in combining the publications to achieve the claimed invention; and the publications must teach or suggest all of the claim limitations. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP § 2142. In analyzing obviousness, the Court of Appeals for the Federal Circuit has repeatedly cautioned that:

[t]he factual inquiry... must be based upon objective evidence of record.... [T]he best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is **rigorous application** of the requirement for a showing of the teaching or motivation to combine prior art references.... [P]articular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.

In re Sang-Su Lee, 277 F.3d 1338, 1343 (internal citations omitted; emphasis added).

The Examiner begins the obviousness rejection from the following proposition: “where claimed products and the prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established.” Paper No. 11, page 6. The conditions under which the burden may be shifted to applicants to prove no anticipation by a publication are described in *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977):

Where... the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can

require an applicant to prove that the prior art products do not necessarily possess the characteristics of his claimed product.

The Examiner, however, has not met the conditions recited in *Best*. For example, the Examiner purports to support the rejection by asserting as “fact” something that is clearly incorrect: that “Sounik et al claims the same mixture of compounds to form the same particles as Applicants.” Paper No. 11, page 7. This statement is inconsistent with the Examiner’s own statement that “Sounik et al is deficient in that it does not specifically teach the use of either ‘dimethylhexylvinylsiloxide’ or ‘trihexylsiloxide’” as required by the instant claims. Paper No. 11, page 7. Moreover, if the Examiner’s alleged “fact” were true, the rejection would be for anticipation, not for obviousness. Other deficiencies in the Sounik et al. primary reference are addressed with the assistance of the following table:

Applicant’s Claim language:

Deficiencies in Sounick et al.:

30. A fluorescent particle comprising:

The cited publication does not disclose any particles. Rather, the publication refers to, *e.g.*, mixing dyes with polymers and heating until a melt phase is formed, which can be molded into “suitable shapes.” The Examiner has never indicated how the term “particle” is being interpreted to include any compositions within the cited publication. This “melt” method is not “identical or substantially identical to the processes used in the instant specification” to form fluorescent particles.

Furthermore, the publication is silent as to fluorescence of the compositions, and nothing of record indicates that dyes, when formed by melting into polymers in this

fashion, would retain any fluorescent properties.

a. a first compound selected from the group consisting of silicon phthalocyanine bis(dimethylhexylvinylsilyloxy) and silicon phthalocyanine bis(trihexylsilyloxy); and

The cited publication does not disclose any composition having the claimed compounds, much less two such compounds in the same particle, as required by parts (a) and (b) of the claim.

b. a second compound that is a bis(dimethylhexylvinylsilyloxy)-substituted or bis(trihexylsilyloxy)-substituted phthalocyanine, naphthalocyanine, or anthranilylocyanine derivative, or a bis(dimethylhexylvinylsilyloxy)-substituted or bis(trihexylsilyloxy)-substituted hybrid phthalocyanine derivative.

Based on the foregoing, Applicants respectfully submit that the claimed and prior art products are not identical or substantially identical, nor are they produced by identical or substantially identical processes. Indeed, seemingly in acknowledgement of this fact, the Examiner relies on the secondary Wheeler *et al.* publication, which allegedly discloses silicon phthalocyanine bis(trihexylsiloxy) and silicon naphthalocyanine bis(trihexylsiloxy). However, the dyes of Wheeler *et al.* are **not** combined as components of any single particle. but rather are used separately in solution. The above evidence falls far short of *prima facie* obviousness case. Thus, the attempt by the Examiner to shift the burden to Applicant to disprove a *prima facie* case of obviousness is improper.

Moreover, the Examiner's reliance on the secondary Wheeler *et al.* publication contradicts the assertion that the Sounik *et al.* publication allegedly discloses "the same

compounds” as the instant claims. The assertion is based on an allegation by the Examiner that the dimethylhexylvinylsilyloxy and trihexylsilyloxy substituents recited in instant claim 30, which are attached to a coordinated silicon atom as “axial ligands” in the molecules of the claims (see, e.g., specification, page 15, line 18, through page 16, line 1), are within the scope of the phrase “aliphatic, acyclic, or aromatic substituent containing 1-12 carbon atoms” (recited in claim 9 of the Sounik *et al.* publication). Paper No. 11, page 8. **The phrase cited by the Examiner refers to substituents of the tetraazaporphyrin ring, not substituents of the coordinated silicon atom as alleged.** Thus, this basis for combining the cited art is entirely unfounded. Furthermore, it is unclear why claim 9, which recites “a thin film optical medium,” relates in any way to the claimed fluorescent particles.

The Examiner offers other unsubstantiated and confusing statements in this regard, in spite of the apparent recognition by the Examiner that the molecules disclosed by the primary Sounik *et al.* publication differ from those of the instant claims and from those of the secondary Wheeler *et al.* publication. For example, the Examiner states that “the compounds disclosed by Sounik *et al.* and Wheeler *et al.* would have the same properties because they disclose the SAME COMPOUNDS”.... The compounds have identical structures and thus have identical uses.” Paper No. 11, pages 15-16, emphasis in original.

In attempting to support this assertion, the Examiner points to a statement in the “Background of the Invention” section of the Sounik *et al.* publication, which is merely an acknowledgement that the Wheeler *et al.* publication exists. This statement indicates that the authors of the primary Sounik *et al.* publication were fully aware of the secondary Wheeler *et al.* publication; yet, as evidenced by the fact that such molecules do not appear anywhere in the remaining description or claims of the primary Sounik *et al.* publication, those same authors apparently did not consider the molecules disclosed by the Wheeler *et al.* publication suitable for their purposes. Likewise, the Examiner again confusingly points for support to “claim 9 [of Sounik *et al.*] where X is 6.” Paper No. 11, page 15. As discussed above, the relevance of the substituent “X,” which is on the rings of the tetraazaporphyrin molecule and not an axial ligand attached to the coordinated metal, to either the Wheeler *et al.* publication or the instant claims is entirely unclear. In addition, the trihexylsiloxy substituent referred to in the Wheeler *et al.* publication contains 18 carbon atoms, not 6 as the Examiner apparently believes.

Despite the continued lack of clarity in the rejection, however, Applicants have attempted to respond to the various allegations of the Examiner. The Examiner's response to Applicants remarks attempts to account for the numerous flaws in the asserted *prima facie* case of obviousness. But the Examiner's various responses in this regard evidence a misperception of what constitutes a *prima facie* case of obviousness.

For example, with regard to Applicants' arguments that no particles are disclosed in the Sounik *et al.* publication, the Examiner responds that "one cannot show nonobviousness by attacking references individually." Paper No. 11, page 12. This truism of patent law misses the point. The primary Sounik *et al.* publication is cited for its alleged disclosure of particles. The Examiner has not indicated what, if anything, in the Sounik *et al.* publication is a "particle" as that term would be interpreted by one of skill in the art in light of the instant specification. By failing to do so, the Examiner has failed to establish that the combination of references teaches each and every element of the present claims, as required to establish a *prima facie* case of obviousness.

With regard to Applicants' arguments that no fluorescent particles are disclosed, the Examiner responds that the Wheeler *et al.* publication discloses that the molecules cited therein are fluorescent and that, in any case, such a property is inherent in the molecules. Paper No. 11, 13. This begs the point of Applicants' arguments. The Wheeler *et al.* publication discloses the fluorescence of silicon phthalocyanine bis(trihexylsilyloxy) in a dichloromethane solution. But, when the publications are combined as suggested by the Examiner, that molecule will no longer be in solution; it will be in, *e.g.*, a homogenous solid generated from a melt phase. Nothing of record indicates that the molecules disclosed in the Wheeler *et al.* publication would be fluorescent when mixed with a polymer, melted to homogeneity, and formed into a solid as described by the Sounik *et al.* publication. And that method of forming a solid is not "identical or substantially identical to the processes used in the instant specification" to prepare fluorescent particles. The burden remains with the Examiner to establish by some objective evidence that the solids of the Sounik *et al.* publication prepared using the dyes of Wheeler *et al.* would be (inherently) fluorescent. Thus again, the Examiner has failed to establish that the combination of references teaches each and every element of the present claims, as required to establish a *prima facie* case of obviousness.

Applicants also noted in their remarks that, in order to arrive at the instant claims, the Examiner cannot simply place one of the individual molecules allegedly disclosed by the Wheeler *et al.* publication into a particle; instead, the Examiner must provide a motivation to place two of the molecules disclosed by the Wheeler *et al.* publication in a single fluorescent particle in order to provide the instantly claimed invention, despite the fact that both publications are silent as to providing any such combination. Thus, the artisan must:

- (i) select a molecule in the Sounik *et al.* publication comprising an aliphatic ligand (Z),
- (ii) modify the aliphatic group to provide a trihexylsiloxy group according to the disclosure of the Wheeler *et al.* publication,
- (iii) select two such ligands (Z) on the molecule,
- (iv) combine the molecule with a second molecule that is also selected to include each of (i)-(iii), and
- (v) provide this combination as a fluorescent particle.

The Examiner has responded to this argument with the assertion that “‘motivation’ does not have to be provided for ‘each’ molecule as Applicants contend because ‘there is no requirement that the prior art provide the same reason as applicant to make the claimed invention.’” Paper No. 11, page 12. This again shows a misunderstanding of Applicants’ arguments. The instant claims refer to a particle having two compounds, each of which comprises dimethylhexylvinylsiloxy or trihexylsiloxy. The only two such molecules in the asserted *prima facie* case are the trihexylsiloxy-containing molecules allegedly disclosed in the Wheeler *et al.* publication. Whatever motivation is proposed by the Examiner, it must provide a reason that the skilled artisan, with no knowledge of the claimed invention, would have selected the claimed components for combination in the manner claimed; that is, there must be motivation to provide two different fluorescent molecules, each of which comprises dimethylhexylvinylsiloxy or trihexylsiloxy, in a single fluorescent particle. By failing to provide a motivation to combine two of the molecules allegedly disclosed by the Wheeler *et al.* publication into a single particle, the Examiner has clearly failed to establish a *prima facie* case of obviousness.

The possible motivations suggested by the Examiner for combining the cited publications in any fashion are as follows: that the Wheeler *et al.* publication states “[t]he presence of trialkylsiloxy groups on the central Si atom leads to relatively high solubility in these compounds and permits studies of solutions of them at the millimolar level”; and that “Wheeler et al shows that the compounds are stable and exhibit favorable optical properties that are required [by] Sounik et al” and that “Wheeler et al further shows states [sic] that the compounds show high thermal and chemical stability and interesting... optical properties.” Paper No. 11, pages 8-9. Applicants respectfully submit that none of these possible motivations would lead the skilled artisan, with no knowledge of the claimed invention, to combine two molecules, each of which comprises dimethylhexylvinylsilyloxy or trihexylsilyloxy, into a single fluorescent particle as required by the instant claims.

The first of these asserted motivations involves the statement in the Wheeler *et al.* publication that the presence of trialkylsiloxy groups on the central Si atom of phthalocyanines would provide sufficient solubility to “permit studies” of such molecules. This statement is an indication that the properties of such molecules are not well established, and may be unpredictable. Contrary to the Examiner’s assertion, Applicants’ argument does not involve “an unsubstantiated statement that the [Wheeler] reference is not enabled.” Paper No. 11, page 14. The Wheeler *et al.* publication is a scientific publication that discloses certain limited properties of silicon phthalocyanine bis(trihexylsilyloxy). Whatever these properties were, the authors of the primary Sounik *et al.* publication were fully aware of them; indeed, as the Examiner has noted, the Wheeler *et al.* publication is referred to in their “Background of the Invention.” Yet the molecules disclosed by the Wheeler *et al.* publication are not referred to anywhere in the Sounik *et al.* publication as being suitable for the purposes disclosed therein. Based on these facts, the skilled artisan would likely infer that such molecules, the properties of which are not well established, are likely not suitable for use in the methods disclosed by Sounik *et al.*, and would not have had a reasonable expectation of success in combining the publications as the Examiner contends.

The second and third of the asserted motivations concerns an allegation that the molecules disclosed in the secondary Wheeler *et al.* publication exhibit favorable chemical and optical properties that are required by the primary Sounik *et al.* publication. The Examiner

quotes page 2, lines 43-44, of the Sounik *et al.* publication, which states that the compositions disclosed therein “[exhibit] light absorption over a spectrum range of about 660-860 nm” (emphasis added). Such light absorption properties are shown, *e.g.*, in Figs. 1 and 2 of the Sounik *et al.* publication, which show absorption over this entire range. In contrast, the molecules disclosed by the Wheeler *et al.* publication do not exhibit this property, losing absorption strongly around 750 nm. *See, e.g.*, Wheeler *et al.*, Table 2 and Fig. 8. This is perhaps the reason that the molecules disclosed by the Wheeler *et al.* publication are not referred to anywhere in the Sounik *et al.* publication as being suitable for the purposes disclosed therein. Importantly, use of the compounds disclosed by the Wheeler *et al.* publication as a mixture according to the Sounik *et al.* publication would render the mixture unsatisfactory for the purposes intended by Sounik *et al.*, as light absorption would not occur over the desired range of wavelengths. *See, e.g.*, MPEP 2143.01 (the proposed modification cannot render the prior art unsatisfactory for its intended purpose).

Applicants respectfully submit that, when the cited publications are properly considered, it is apparent that any motivation to modify or combine the cited publications in order to provide the instant claims can only be gleaned in hindsight using the instant specification as a guide. In the absence of the teachings of the instant application, the skilled artisan would not have a motivation to combine the publications as the Examiner contends. Because a motivation to modify the cited art must be found in the prior art, and not in applicant’s own disclosure, no *prima facie* case of obviousness has been established. *See, e.g., In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP § 2142.

Further compounding the flaws in the rejection, the Examiner also exhibits a misunderstanding of how evidence of unexpected properties is to be considered. Applicants have submitted evidence that the claimed fluorescent particles exhibit unexpected properties that overcome any *prima facie* case of obviousness that may have been established by the Examiner. Specifically, when the dye pairs are included in a single particle, fluorescence energy transfer (“FET”) occurs between the members of the dye pair. In FET, all or a portion of the energy absorbed by one member of a dye pair (the “donor”) is not emitted as detectable emission light by that member; instead, the energy is “transferred” to the second member of the dye pair (the “acceptor”) and emitted at the longer emission wavelength of the acceptor. As described in the

instant specification on page 40, lines 10-19, FET was confirmed in the particles of the instant invention by liberation of the dyes and measuring the loss in emission intensity of the acceptor dye. The FET parameters of the particles of the present invention are described in detail in the Example beginning on page 43, line 21. In addition, as described in the instant specification on page 87, incorporation of tetraazaporphyrin dyes in particles can result in dramatic quenching of the fluorescence signal. The use of axial ligands such as bis(dimethylhexylvinylsiloxide) can dramatically reduce this quenching.

The Examiner's response that "the features upon which applicant relies... [are] not recited in the rejected claims" demonstrates that the Examiner has failed to properly consider Applicants' evidence. The unexpected properties are provided by incorporating the claimed combination of molecules into a fluorescent particle. Thus, the features upon which Applicants rely most certainly are recited in the instant claims. These advantages are described in detail in the instant specification, and must be considered by the Examiner. *See*, MPEP § 2144.08(II)(B) (it is error not to consider evidence presented in the specification). Moreover, the Examiner's unsupported assertion that such properties are "inherent" in the compounds is contrary to the law which requires that unexpected properties be measured relative to the closest existing prior art, and not to a combination of publications as suggested by the Examiner. *See In re Boesch*, 205 USPQ 215 (CCPA 1980). The compounds of the instant claims are disclosed in the prior art only as individual molecules; the fact that the unexpected properties might be "inherent" once they are combined in a fluorescent particle is immaterial to the consideration of the unexpected properties. Applicants respectfully submit that, by failing to properly consider Applicants' evidence in this regard, the Examiner has not considered the record as a whole.

Because no *prima facie* case of obviousness has been established by the Examiner, or, in the alternative, because any *prima facie* case of obviousness has been rebutted by a showing of unanticipated properties of the claimed invention, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103.

Applicants also respectfully traverse the rejection of claims 31 and 45 as allegedly being unpatentable under 35 U.S.C. § 103(a) over Sounik *et al.* and Wheeler *et al.*, *J. Am. Chem. Soc.* 106: 7404-10 (1984) in further view of Vener *et al.*, *Anal. Biochem.* 198: 308-311 (1991).

Applicants submit that the Examiner has not established a motivation to combine the publications as suggested by the Examiner.

The Sounik *et al.* and Wheeler *et al.* publications are discussed in detail above. The Vener *et al.* publication is cited solely for its disclosure of latex particles of 1.8 μm in diameter for use in hybridization assays.

Previously, the Examiner contended that the skilled artisan would allegedly be motivated to use the “dyes” disclosed by the Sounik *et al.* and Wheeler *et al.* publications in latex particles because “Sounik *et al.* and Wheeler *et al.* teach that these dyes are highly water soluble, stable and possess favorable fluorescent properties.” Paper No. 9, page 14. In response to Applicants’ arguments, the Examiner has now dropped this line of reasoning from the rejection, stating that “it does not matter whether the compounds are water-soluble or not and does not need to indicate a relationship to water solubility. Shifting the basis for the rejection, the Examiner instead now relies on the assertion that “Sounik *et al.* and Wheeler *et al.* teach that the ‘dye mixture can be formed in a homogenous blend with a polymer’ and since latex disclosed by Vener is a ‘polymer’ a person of skill in the art would have been motivated to combine these references.” Paper No. 11, page 20. Applicants respectfully submit that this new line of reasoning represents a clear hindsight-based combination of publications by the Examiner.

First, as discussed in detail above, the Examiner is incorrect that “Sounik *et al.* and Wheeler *et al.* teach that the ‘dye mixture can be formed in a homogenous blend with a polymer.’”. With regard to latex itself, there are literally thousands of polymers available to those of skill in the art, and the Sounik *et al.* and Wheeler *et al.* publications never mention latex. Furthermore, nothing of record indicates that latex would be suitable in the compositions disclosed by the Sounik *et al.* publication (*e.g.*, a latex-based optical recording medium?). What is missing from the asserted *prima facie* case of obviousness is any reason that the skilled artisan, with no knowledge of the claimed invention, would have selected the claimed components for combination in the manner claimed to arrive at a fluorescent latex particle. Moreover, the skilled artisan would readily acknowledge that “latex” is a colloidal dispersion of small (*e.g.*, submicroscopic) particles. In contrast, the Sounik *et al.* publication refers to manufacture of dye/polymer blends by melting and molding. Applicants previously requested that the Examiner

cite some supporting evidence for the use of the materials referred to in the cited publication for the formation of latex particles. The Examiner has apparently declined this request or has been unable to find such evidence.

As discussed above, no motivation has been established to combine the Sounik *et al.* and Wheeler *et al.* publications as suggested by the Examiner. The Vener *et al.* publication does not correct the flaws in the *prima facie* case of obviousness. Because no *prima facie* case of obviousness has been established by the Examiner, or, in the alternative, because any *prima facie* case of obviousness has been rebutted by a showing of unanticipated properties of the claimed invention, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103.

Obviousness-type double patenting

Applicants continue to acknowledge the obviousness-type double patenting rejection of claims 30-31, 42, and 45. Should the claims be found allowable as presently written, a terminal disclaimer will be submitted.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the address and telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,
FOLEY & LARDNER

Dated: December 2, 2003

By: Barry S. Wilson
Barry S. Wilson
Attorney for Applicant
Registration No. 39,431

P.O. Box 80278
San Diego, CA 92138-0278
Voice: 858-847-6700
Fax: 858-792-6773